

# Clinical neurology <sup>6</sup>

## A review

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The past decade has seen major advances in all areas of medicine but in none has this been more evident than in neurology. Given the breadth of the speciality this is perhaps not surprising but a more important factor concerns those advances in other scientific fields that have impinged upon neurology. Disciplines as disparate as physics, mathematics, computer technology, engineering, psychology and a host of biological specialities, especially nucleotide chemistry, have all had a profound effect. The vast amount of new data accumulated leaves the clinician bewildered when confronted with a patient complaining of neurological symptoms: what is the explanation of the phenomena exhibited, how does one investigate this patient and what is the appropriate treatment? This review is an attempt to highlight some of the advances which the author thinks important in that they have led, or will lead, to a better understanding, and hopefully better treatment, of the patient with neurological disease.

I will consider three major areas, namely, transmissible diseases of the nervous system, nuclear magnetic resonance applied to neurology, and neuropsychology. It is in these areas that major advances have been made in the past decade and which will continue into the next. One additional area of importance is genetics with the use of DNA technology to dissect the blueprint of faulty instruction; however this has recently been reviewed in this journal (*J. Roy. Coll. Physicians*, 22, 212) and is therefore not discussed further, although it is work of merit. At the end of this review there is a short discussion of some other areas of neurology, eg PET scanning and neurochemistry.

The reader will immediately recognise that large areas, indeed the major part of neurology, are not mentioned. This is partly due to ignorance on the part of the author but many omissions are deliberate. Numerous papers on neurological topics are published every day; some are erroneous, some mundane and most are published prematurely. As an example one only has to look at the continuing struggle to disentangle the immunological abnormalities found in multiple sclerosis, a struggle that shows every sign of continuing to progress down blind alleys. There will be no mention of these. Also omitted are subjects such as myasthenia gravis where significant advance continues but the basic principles of the disease processes are sufficiently understood by clinicians that it is superfluous to discuss them in detail.

## Neurological disorders due to transmissible agents

The past fifteen years have witnessed a better understanding of the pathogenesis of two groups of diseases, initially thought to be degenerative, and now known to be due to transmissible agents, namely, retrovirus and prion induced neurological diseases.

### 1. Retroviruses

Before 1980 the practising physician may never have heard of retroviruses particularly in relation to the nervous system. On the other hand his contemporary in veterinary medicine will have learned of several diseases caused by retroviruses and will have been all too familiar with the fact that retroviruses broadly cause two types of disorder, namely, tumours (feline, bovine and murine leukaemia viruses) and neurological disease (feline and murine leukaemia viruses, equine infectious anaemia, visna, and caprine arthritis encephalitis viruses). For the medical clinician all this has changed in the past eight years.

At least four retroviruses have been discovered to be pathogenic in man; HTLV1, HTLV2, HIV1, HIV2. Two of these have been connected with neurological disorders.

#### HTLV1

HTLV1 was the first retrovirus of humans to be described and was found to cause adult T-cell leukaemia (ATL). More recently it has been shown to be associated with, and almost certainly causes, a paraparetic disorder of slow evolution in a variety of populations, especially in Japan and the Caribbean. In the Afro-Caribbean population the disease is now called tropical spastic paraparesis (TSP) and also occurs in immigrant populations to France and the United Kingdom. In the Orient a disease that is probably identical is termed HAM (HTLV1 associated myelopathy); it is particularly common in southern Japan. There are several other areas of the world, especially the tropics, where the disease occurs but its frequency is uncertain. In 1954, Sigurdsson described a paraparetic illness in Icelandic sheep called visna (wasting) which had a long incubation period (years) and he coined the term 'slow infection.' Subsequently, visna was one of the first diseases to be shown to be due to a



retrovirus, ie the virus contained a reverse transcriptase enabling viral DNA to be produced from genomic viral RNA. Its pathology in many respects is similar to that in TSP. In both sheep and man there is an intense inflammatory exudate in the cord and meninges with demyelination in the corticospinal tracts and dorsal columns.

Clinically, patients with TSP develop radicular pain in the legs and pain in the lumbar region associated with a progressive paraparesis and sphincter disturbance. There may be periods of apparent cessation of progression but most patients become severely disabled over a decade or so. Unlike multiple sclerosis (MS), which is rare in the populations where TSP occurs, significant upper limb involvement is unusual and magnetic resonance images (MRI) of the brain and spinal cord show little evidence of extensive plaque formation in the white matter or periventricular areas, although atrophy of the dorsal cord is typical. Interestingly, evoked potentials in the visual, auditory and somato-sensory domains are abnormal in 50% of TSP patients (lower in Orientals) and the cerebrospinal fluid (CSF) has evidence of local immunoglobulin synthesis. All these features have long been known but since the initial paper by Gessain and colleagues from Martinique, it is clear that most, if not all, patients with TSP have high titres of HTLV1 specific antibodies in the blood and CSF, and the oligoclonal bands in the CSF contain either HTLV1 specific IgG or IgM immunoglobulins. Furthermore, it has been shown that lymphocytes contain, and express, HTLV1 virions. Another feature of retroviruses is their ability to integrate viral specific DNA into the genome of the host, thus rendering it invisible to the host immune system. This certainly occurs in the case of HTLV1. If the DNA sequence of a virus is known, as in HTLV1, it is possible to place small segments of the DNA into a mass of host DNA containing HTLV1 and detect the presence of the virus by the polymerase chain reaction (PCR). In this technique a thermophilic polymerase will replicate a DNA sequence, provided it is annealed to a sequence of complementary DNA, and it will do this repeatedly until vast numbers of copies are produced. These copies will only be produced if an appropriate sequence was present in the first place. All cases of TSP who are HTLV1 antibody positive have such integrated HTLV1 DNA.

The question arises how the patients acquire their infection and then the disease. In Japan, extensive epidemiological studies of ATL suggest acquisition of the retrovirus by children from their mother in the perinatal period and first three years of life since a considerable proportion of children of infected mothers, but not fathers, become sero-positive over this period; thereafter sero-conversion ceases until late teens when it progressively increases. Furthermore, it is known that adult female spouses of infected men have a high prevalence of sero-positivity and conversely husbands of infected women have a low prevalence. Finally, blood transfusion was formerly a potent route of transmission. All these data are consistent with transmission by a transplacental route or suckling, and later by sexual contact. Data from the UK in families of patients with TSP are consistent with this hypothesis. Again a lot more is known about

transmission of animal retroviruses, especially visna. Here transplacental infection rarely occurs (placentation is different between ungulates and primates); lambs are infected from their dams by early close contact and suckling.

HTLV1 shares with other retroviruses the extraordinary ability to cause more than one disease yet leaving the majority of the infected population asymptomatic. Why do some patients develop ATL and others TSP? Obviously, in the case of a rapidly fatal disease like ATL, there is a bias against subsequently having TSP but the converse does not apply, yet there is only one documented case of a patient with both conditions. One possibility is that there are distinct leukaemia and TSP phenotypes of HTLV1. This definitely occurs in the case of murine leukaemia virus where only certain strains cause neurological disease. However, there is no good evidence of a TSP strain of HTLV1 although some workers have shown nucleotide sequence differences in viruses isolated from TSP and ATL patients in the usually highly conserved reverse transcriptase. Conversely, the type of disease that develops could be host dependent. The Japanese have claimed distinct HLA types in the two diseases but the numbers studied were small compared with the number of potential HLA types. Host genetic factors undoubtedly play a part in determining whether animals get infected with retroviruses, and a paralytic illness is especially common in Icelandic sheep infected with visna virus.

Finally, and perhaps even more remarkable, is the fact that a large number of subjects infected with HTLV1 are asymptomatic. This applies to relatives of patients with TSP in the UK where about a fifth have antibodies but are asymptomatic. Using PCR there is no evidence that relatives who do not have antibodies harbour the virus, thus ruling out the possibility of a ubiquitous infection with only a few subjects exhibiting an antibody response. In general, the antibody titres are low in relatives but this is not invariable. Why the subjects are asymptomatic and whether they will ever develop TSP is unknown, although the lifetime risk of ATL in Japan in such people is not insignificant and in the case of murine leukaemia virus, disease develops in virtually all, provided the animals live for a sufficient period.

While there is good evidence that HTLV1 is associated with TSP, the pathogenesis of the condition is obscure. The inflammatory exudate about the vessels is compatible with an immune attack upon infected cells as is the local immunoglobulin synthesis, expression of interleukin-2 (IL2) on lymphocytes and temporary response to steroids, but we do not know which cells in the central nervous system are infected. How this inflammatory exudate leads to demyelination is even more obscure. In this era of immunological dominance, an immune-based attack upon glia either infected with HTLV1 or exhibiting a common epitope is attractive and in accord with conventional wisdom. Indeed, one could argue that the very high antibody titres to HTLV1 found in TSP direct, in some way, lymphocyte attack upon an antigen (a type of *in vivo* antibody-dependent cell mediated cytotoxicity), but unless the target cell were the oligodendrocyte (the myelinat-



ing cell of the CNS) it could not directly cause demyelination. As in MS, a weak hypothesis of by-stander demyelination, where an inflammatory response releases cytokines and enzymes that damage adjacent myelin, has been put forward. If such a system does exist it will be necessary to explain why in visna every infected animal has extensive inflammatory exudates in the CNS, but demyelination with paraparesis may take years to develop and may never occur. Clearly, there is much work to be done here; a sufficient explanation must, having satisfied the above, also account for the target organ being the cord rather than the brain.

### *HIV1*

Another retrovirus that infects man is HIV1. It was soon realised that this agent caused CNS disease in terms of opportunistic infections but the medical clinicians were slow to recognise that the virus, which is fairly closely related to visna, was neurotropic and that it could directly cause neurological dysfunction.

Clinically, two types of primary CNS disorder occur in HIV1 infection. First, at the time of sero-conversion soon after acquisition of infection, some subjects develop an acute meningoencephalitis characterised by fits, confusion and meningitic signs, and occasionally myelitis. These symptoms resolve and their significance in predicting further CNS disturbance is unknown. Second, several different chronic syndromes occur in patients with long-standing HIV infection. Cortical disturbance comprising progressive dementia affects a substantial number of patients with acquired immuno-deficiency syndrome (AIDS) and may occasionally precede any opportunistic infections in HIV1 infected patients. There is a sub-acute encephalitis with diffuse leukoencephalopathy or patchy myelin pallor, accumulations of large astrocytes and distinctive giant multi-nucleate cells which probably arise from histiocytes harbouring the virus. Blood vessels calcify, especially in children. Ultimately, the patient is severely demented and helpless. Less commonly a myelopathy occurs although again there is dispute concerning its frequency. Clinically, it is similar to subacute combined degeneration of the cord with progressive paraparesis and posterior column loss. Pathologically, there is vacuolar change, especially in the lateral and posterior parts of the dorsal cord. Combinations of the myelopathy and cortical disturbance have been reported to be common at autopsy by some, but not all, authors.

CNS infections are common as a consequence of the HIV1 induced immuno-suppression. Toxoplasma and cytomegalovirus are extremely frequent while fungal infections are unusual, although this depends to some extent upon the areas from which patients come. Papova virus infection causing progressive multi-focal leukoencephalopathy is common. Less frequently, bacterial infections also occur, especially mycobacterial meningitis.

Of great theoretical interest is the occurrence of B-cell lymphomas in the CNS. Primary lymphomas (formerly called microgliomas) are rare tumours of the brain but occur more frequently in the immuno-suppressed, such as renal transplant patients, than in the normal population.

The advent of HIV1 infection has resulted in a large increase in the numbers of such tumours in the USA with the suggestion that, within a decade, they could become the commonest primary brain tumour. Presumably they arise because of impaired immune surveillance of rogue cells and the moderately immunologically privileged CNS is particularly sensitive to such inattentiveness. In practical terms, any patient with HIV1 infection who has an intracerebral mass should be treated for toxoplasmosis and a biopsy done only if there is no improvement. The prognosis for primary brain lymphoma is poor.

Abnormality of the peripheral nervous system is less well documented. An acute or subacute inflammatory polyneuropathy occurs in some patients with HIV1 infection and some recover from their neurological illness like any other patient with Guillain-Barré syndrome. The pathology is predominantly segmental demyelination. Patients with AIDS also develop a mainly sensory axonal polyneuropathy and occasionally mononeuritis in the limbs or cranial nerves occurs. HIV1 has been isolated from peripheral nerves. A myositis has been described.

### *Other retroviruses*

No other retrovirus has been conclusively shown to cause neurological disease in man. Inevitably, since neurology has so many diseases of unknown aetiology, extensive trawling for retroviruses has been carried out. Equally predictably, MS has been the disease where involvement of HTLV1-like retroviruses has been claimed. For example, in two populations of MS patients, one in the USA and the other in Sweden, antibodies to part of the HTLV1 genome have been detected and more recently there have been claims that fragments of the genome itself exist in patients' cells. However, there is no convincing evidence that HTLV1 is involved in MS. One of the problems with MS is the fact that patients produce antibodies to many common viruses in excessive amounts as an anamnestic response. HTLV1 and other retroviruses seem to be no exception; there are even HTLV1 specific oligoclonal bands in the CSF. Why patients in Europe should have such competent immune cells is unknown, but since an increasing number of endogenous retroviruses are being found on screening patients, it is quite possible that all these tests pick up common epitopes between unknown and recognised retroviruses. In 1989 a retrovirus is as good a candidate as any as an aetiological agent for MS, but the reader is advised that one candidate of yesteryear, namely, *Mycobacterium tuberculosis*, seemed so good that old tuberculin was injected intrathecally (without benefit)! In spite of this note of pessimism, the next decade must surely see the discovery of retroviral causes of other neurological diseases.

## **2. Prions**

Scrapie in sheep, bovine spongiform encephalopathy, Aleutian mink disease, kuru and Creutzfeldt-Jakob disease (CJD) have similarities. All are apparently degenerative, yet infectious, conditions and in some there is a familial tendency. Many now believe that they are caused



by a peculiar transmissible agent, the prion.

CJD is the archetype of the exotic neurological disease in which a vast variety of apparently inexplicable signs occurs such as amyotrophy, myoclonus, intellectual decline, agnosia, cortical blindness, spatial neglect etc, so beloved of the *prima donna* neurological consultant and feared by students, not to mention more senior staff of another ilk. It had long been realised that the diagnosis of CJD did not indicate a single entity. One group of patients did, however, have a uniform clinical picture, with an onset in later life of ataxia, rapid intellectual and cognitive decline, myoclonus and an EEG with periodic complexes. All died within two years and all had a characteristic spongiform change in the cortex and extensive gliosis of the cortex and cerebellum. In addition, amyloid was present within the CNS, a point that led Nevin to think the disorder was primarily vascular. It was clear that several patients with this picture had previously had neurosurgical operations and in 1968 this form of the disease was experimentally transmitted, after a long incubation period (1-2 years), to chimpanzees. Subsequently, there has been transmission by transplantation of human tissue such as cornea and human pituitary growth hormone. No other form of CJD has been transmitted with the exception of a more chronic ataxic type known eponymously as Gerstmann-Straussler-Scheinker syndrome.

Kuru is a disease formerly found in isolated cannibalistic tribes of New Guinea. Its pathology is similar to CJD, especially in the cerebellum. It is transmissible to animals but there has been debate about its transmission in New Guinea: Gajdusek believes cannibalism is important, especially the ingestion of parts of the CNS of infected subjects.

These two diseases have come to the fore with the discovery of the prion (proteinaceous infectious particles, not the Antarctic petrel!), considered by some, especially Prusiner, to be the infective agent responsible for transmission and pathogenesis of these diseases in man and of scrapie in ungulates. All normal neurones contain the glycoprotein PrP<sup>c</sup> but an aberrant form, PrP<sup>sc</sup>, which is resistant to protease digestion, has been found in cells from scrapie and CJD. There is evidence that the protein, which occurs as twisted fibrils, can transmit scrapie, and furthermore, the amyloid found in the CNS of patients with CJD comprises prion protein. No nucleic acid has been demonstrated in prions, implying that they are most unusual infective agents. How such an agent can cause disease and why some patients have a family history is unclear, although it is possible that the DNA coding for normal PrP<sup>c</sup> is altered. One interesting point about scrapie, kuru and CJD is the lack of inflammatory response in the CNS. This could be explained by the fact that the infectious prion protein is similar to the normal protein and is therefore not able to generate an immune response because it is recognised as self.

### Nuclear magnetic resonance

The clinician who relies heavily upon imaging techniques can be excused the feeling that he is constantly having to

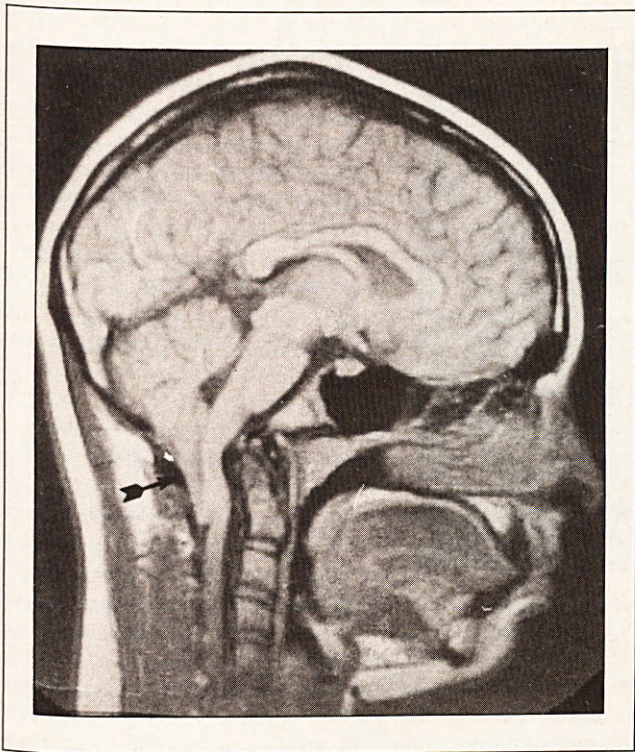
delve into old dust-covered sixth form texts to understand even the words used in the radiology department. Those dry Fourier expressions from physics and maths and nuclear magnetic resonance beloved of physical chemistry masters suddenly come to life and have clinical application. Computerised axial tomographic imaging is commonplace and need not concern us here; it is the technology of the seventies and now part of the standard armamentarium of the clinician. On the other hand, nuclear magnetic resonance (NMR) is the technology of the eighties which will continue to develop over the next few years and must be discussed.

The suggestion that atomic nuclei have magnetic moments was made in 1924 by Pauli and later proved by Rabi. In the mid-1940s, NMR was observed in bulk material by Bloch and Purcell. Later it was realised that the precise frequency at which a nucleus would resonate was dependent upon the chemical environment (chemical shift) and this forms the basis of the commonest use of NMR, namely, high resolution spectroscopy. Such a use in medicine is beginning, particularly the use of phosphate NMR, and may well enable us usefully to study metabolism *in vivo* in man. It is fortunate that phosphate is an important component of metabolic energy pathways and it is already possible to detect the various forms of energy rich phosphate in muscle and brain and to show gross abnormalities in some disorders. Eventually, the formidable problems of precisely locating the sites of abnormality will be overcome and a combination of spectroscopy with the second and, to clinicians, better known use of NMR, namely imaging, will become available.

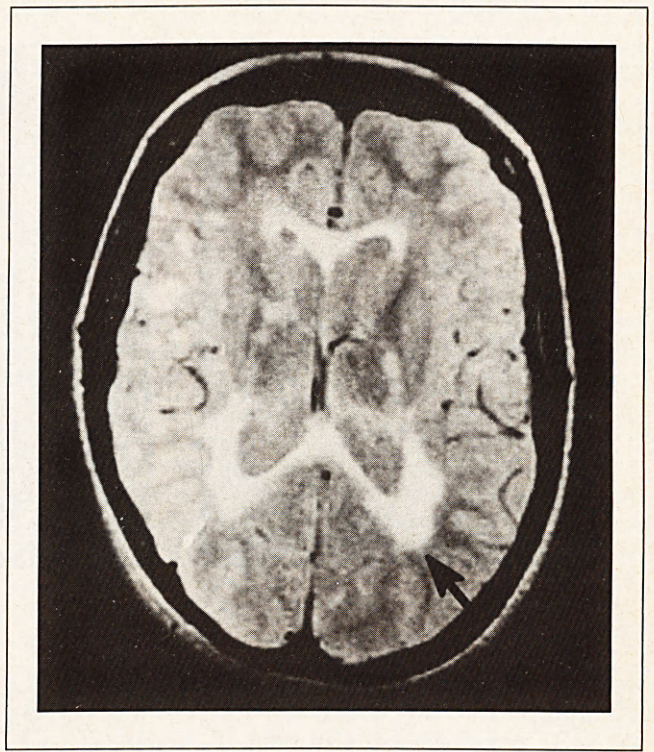
NMR imaging, now called magnetic resonance imaging (MRI), uses the resonance of protons to produce images. Since water is the major component of most living tissue, including the nervous system, a proton image of the brain and spinal cord is primarily a water content picture. This is not the place to discuss the principles of MRI other than to state that protons lined up in a large magnetic field can be forced to precess by a field of appropriate frequency applied at right angles to the first, much like a spinning top will precess. If the second field is turned off, the protons will return to their former equilibrium position, the return being described by two time constants, one longitudinal (T<sub>1</sub>) the other horizontal (T<sub>2</sub>). The energy emitted during the process can be detected. To obtain a topographic map, a magnetic gradient is placed across the tissue under study; the gradient will alter the precise frequency necessary for precession and therefore the site of the signal emitted can be determined.

In straight imaging terms, excellent definition is obtained. The images are free of bony artefact since bone contains little water. The resolution is particularly good in the posterior fossa where CT scanning is poor and is excellent at the level of the foramen magnum, an area that formerly required invasive myelography and CT scanning to detect eminently treatable conditions such as tonsillar herniation (Fig. 1). Similarly anatomical definition of the spinal cord, especially in the cervical region, is good and the development of special receiver coils will





**Fig. 1.** MRI showing tonsillar herniation (arrow). Note tongue of cerebellum extending well below odontoid and kink in medulla.



**Fig. 2.** MRI of cerebral hemispheres in patient with MS. The white signal is abnormal and is particularly prominent around the occipital horns (arrow). Note isolated lesions in cortical white matter on left of illustration.

improve upon a technique that has already largely replaced myelography.

Of greater interest however is the ability to visualise the internal structure of the CNS and to detect pathology. CT scanning was the first technique that gave a non-invasive way of seeing the brain, enabling visualisation of structures such as basal ganglia, internal capsule, grey and white matter; MRI is a vast improvement upon this, showing brainstem structures such as the red nuclei, some pontine nuclei and subdivisions of the substantia nigra. Similarly, pathological events within the brain substance can, in general, be seen with greater clarity on MRI than CT, and certain abnormalities such as demyelinating plaques in MS, areas of demyelination as in leukodystrophies and vascular events are only convincingly seen in the majority of patients on MRI.

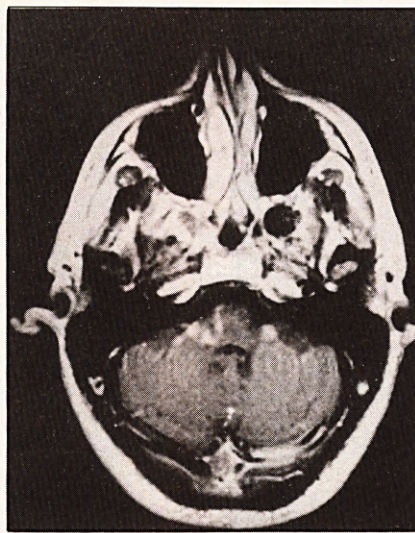
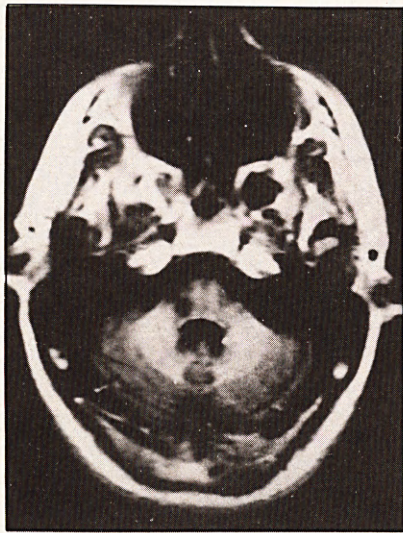
The success of MRI in diagnosis is mostly clearly seen in MS and discussion will be confined to that disease. Plaques of demyelination are demonstrated because there is an increase in water content, initially due to oedema and later to gliosis. MRI is now the investigation of choice of patients suspected of having MS. A high proportion (greater than 95%) of patients with clinically definite MS have localised areas of abnormal signal on brain MRI in the white matter of the cerebral hemispheres, corpus callosum and brainstem and to a lesser extent of the cerebellum, together with abnormal signal return from the periventricular regions, especially the trigone and occipital horns (Fig. 2). The periventricular

abnormality is characteristically irregular. The abnormalities are seen on both T<sub>1</sub> and T<sub>2</sub> weighted sequences, the latter usually being employed. Cord lesions are also seen as irregular areas of increased signal return but are more readily detected from the cervical than the dorsal region.

Of greater clinical interest is the number of patients who have symptoms or clinical signs of a single lesion in the CNS, eg cord, optic nerve, brainstem, which could be the prelude to MS. In these, there is evidence of multiple lesions in the brain identical to those seen in established MS in 50–70% of patients at presentation. More patients with multiple lesions on MRI compared with none do go on to develop clinically definite MS and this is especially true if there is evidence of abnormal immunoglobulin synthesis in the CNS. Having said all this, there is nothing pathognomonic of MS on MRI. Scans similar to MS can be found in a wide variety of diseases including the leukodystrophies, hereditary ataxias, encephalitis, and vascular disease although in general there are pointers to the diagnosis of MS in the morphology of the lesions, eg extensive damage in the corpus callosum, the irregularity of the periventricular change. The diagnosis, however, remains a clinical one.

The cause of the abnormal signal return in MS is not entirely clear apart from the fact that it indicates increased water content. Experiments with local cold injury to the cortex of cats have demonstrated that the initial abnormality is increase in T<sub>2</sub> and to a lesser extent T<sub>1</sub>,





**Fig. 3.** MRI of posterior fossa in patient with MS illustrating gadolinium enhancement. At left is unenhanced scan showing lesion (dark) in pons at point of entry of eighth nerve on the left side of brainstem. At right enhancement (white) is seen and an additional lesion on other side is apparent. Patient developed deafness 3 days before scan.

due to cerebral oedema which resolves quite quickly. No abnormality is then detected on MRI. After a few weeks the MRI again becomes abnormal,  $T_1$  becoming markedly increased compared to  $T_2$ . Histological studies of these lesions show that gliosis has occurred and the increased water content is now within the astrocytes. The explanation for the differences in imaging characteristics early and late after injury could be that the physico-chemical environment, especially the protein content, of the imaged water only affects transverse relaxation ( $T_2$ ) since  $T_2$  is markedly shortened by interaction with spins of the other molecules.  $T_1$  is independent of the immediate environment of spinning atoms.

Other work in man has shown that early in the generation of a new lesion there is damage to the blood brain barrier. This has been shown using gadolinium (Gd) DTPA enhancement; this is a paramagnetic material that markedly alters the imaging characteristics of a lesion by shortening the  $T_1$  relaxation time. Further, the material can only cross the blood brain barrier when this is broken (Fig. 3). It has been shown by serial scanning that such a break, with enhancement of a lesion, resolves over a period of weeks. For this reason not only does Gd enable better resolution of lesions but can assist in assessing their age. At the practical level the potential of using all these techniques to determine the rate of acquisition of lesions in therapeutic trials looks promising.

Future developments will be made with NMR with improvement of resolution of straight imaging, the use of MRI for angiography and ultimately the mapping of metabolic derangement.

### Neuropsychology

The major difference between animal physiology and neurology and neurological disorders in man concerns cognitive dysfunction. While diseases affecting the muscles, peripheral nerve or major central motor and sensory

systems can result in great disability, it is affections of structures subserving higher cortical function that are most devastating. Over the past decade some important work has been done on the breakdown of cognitive function in man, advances which show every sign of continuing. Neurologists have traditionally been diagram makers attempting to locate the lesion. There is merit in this in that such clinical techniques can guide the investigator and occasionally stay the hand of the interventionist. More importantly, such diagrams can help in understanding certain functions of the brain although one should not take too rigid a view about wiring. Modern imaging techniques do give some insight into the mechanism of brain function, especially with the advent of more functional types of imaging, eg PET scanning for looking at oxidative metabolism. Probably of more importance is the development of techniques for monitoring electrical events in the brain whilst performing, or attempting to perform in the case of damaged patients, specific functions. The application of these techniques is just beginning in the area of neuropsychology as will be briefly discussed in the following paragraphs.

### The agnosias

About 100 years ago, Lissauer studied an elderly patient with a visual disorder in which there was failure of recognition of objects seen without any apparent abnormality of the visual sensory system. He coined the term agnosia to describe this extraordinary phenomenon and designed experiments from which he concluded that agnosia could be divided into two types: apperceptive and associative. The former occurs if an adequate percept of an object cannot be made. Associative agnosia is the inability to recognise an object, ie a percept stripped of its meaning. Psychologists usually take the view that only this latter type of defect is true agnosia, the former being a defect of sensory perception. Agnosias were soon recog-



nised in other sensory modalities, eg auditory agnosia in which sounds are not recognised. Subsequently there was a hint that agnosia in a given modality did not necessarily involve all stimuli or objects. Thus within the auditory sphere an agnosia could be confined to meaningful words (pure word deafness) while in the visual modality failure of colour and facial recognition could occur in isolation.

Recently it has been shown in visually agnostic patients that category specificity is not confined to colour and faces. Warrington and her coworkers have found examples of patients in whom there is a grave deficit in recognition of a single class of objects such as buildings, foods, animals, flowers etc, with little agnosia for other classes. Obviously, there are problems in defining what is a class or a set; animals and flowers are also pretty, yellow, smelly etc, but the fact remains that one does find patients with poor recognition of animals but perfect identification of flowers, and other patients who show the reverse. It thus appears that the brain is organised into categorical systems in the visual modality. Imaging techniques have yet to be applied successfully to this type of neuropsychological deficit but it is now abundantly clear that in the case of agnosia for faces (prosopagnosia) the deficit occurs with right posterior lesions.

### *The aphasias*

Knowledge of the aphasias has also advanced as will be illustrated by studies of one particular example. Conduction aphasia is a relatively rare disorder of speech in which there is a profound disturbance of repetition, good comprehension and relatively preserved spontaneous speech produced with few paraphasic errors. In this condition the patient may superficially appear normal yet may be unable to repeat more than one digit reliably (normal subjects can repeat on average seven). It can be argued that this ability is a measure of short-term memory, this memory system having a small capacity and short life. All other memory can be classed long-term memory. Lesions in the region of the dominant angular gyrus, at the junction of the temporal and parietal lobes, are known to be associated with this type of defect.

Of considerable interest is the observation that certain evoked potentials are abnormal in patients with conduction aphasia. In one experiment a sequential series of three digits was presented to the subject either aurally or visually, then after a short interval another digit shown. The subject was asked if the single digit was in the original series. In normal subjects, if the digit was in the original series, a potential could be recorded from the scalp at a latency of 450 ms ( $P_{450}$ ); if not in this series, no potential was seen. In patients with grossly impaired short-term memory, ie conduction aphasia, the  $P_{450}$  was absent or abnormal to auditory presentation but normal to visual presentation of digits. We thus have an electrophysiological correlate of a specific cognitive deficit.

Event-related potentials of this type are not new but previous studies had dealt with less specific tasks. Starr, who conducted the above experiment, had shown many years ago that a potential occurred at 300 ms ( $P_{300}$  or  $P_3$ ) if subjects were asked to identify an aberrant stimulus

among a series, ie an odd tone within a uniform series of tones, and there have been claims that this crude technique will separate demented (no  $P_3$ ) from psychotic (normal  $P_3$ ) patients. The many subsequent reports have added little to Starr's original paper. No doubt other event related potential work will now be done on tasks specific to a patient's deficit; it should be a fruitful area.

### *Disorders of reading and spelling*

There is increasing evidence that reading and spelling can utilise two systems. The first is a phonological system in which words are sounded out and understood phonetically. The second is a lexical system where words are decoded *en bloc* independent of their component phonemes. Many languages, including English, contain numerous irregular words that cannot be read, written or pronounced phonetically—the irregular words. These can extend to extraordinary lengths eg 'yacht'. Equally there are many words in English that can be pronounced phonetically, eg 'animal'.

It has become clear over the past decade or so that acquired disorders of reading and writing can be divided (imperfectly) into those in which regular words are not spelled or read correctly and those in which there is difficulty with the irregular. One way to differentiate the two, apart from giving lists of the two types of word, is to ask the subject to write and read non-words that can be spelled phonetically, eg 'plit'. The anatomical basis of the two types of dysgraphia has been studied by Roeltgen and Heilman using superimposition of CT scans from patients to delineate the common areas of damage. It appears that the phonological dysgraphias occur with lesions adjacent to the Sylvian fissure while lexical dysgraphia is found in patients with higher parieto-occipital lesions. The anatomical basis of the corresponding dyslexia is not known but, perhaps somewhat surprisingly, phonological dyslexia can be associated with lexical dysgraphia.

Disorders of reading are, however, more complex than this in that some patients for example can read only by recognising each letter (letter by letter readers) having lost the wordform recognition mechanism, whereas others have neglect dyslexia ignoring the beginnings of words. This latter type of dyslexia is of particular interest in that the neglect of the beginning of the word is not part of a generalised neglect of the same half of his or her surroundings. Thus a patient can neglect the left half of a word and the right half of the world. The anatomical and physiological basis of these phenomena is unknown but represents a challenge for the next decade.

### **Conclusion**

The reader may, with justification, ask why there has been no, or minimal, reference to those widely published and publicised specialities such as PET scanning and neurochemistry, together with little mention of classical neurophysiology. The reason is that the advances have not been conceptually as exciting and have, on the whole, been disappointing considering the time devoted to them. However, a minor redress is in order.



PET scanning is an enormously expensive procedure that can be conducted in few centres. It enables one to study the fate of isotopes injected into the body to follow oxidative metabolism or to determine the passage of a variety of drugs to dissect complex pathways of neurotransmission. To date the conceptual advances have been limited. Measurement of blood flow and oxidative metabolism following blood vessel occlusion have shown that cessation of blood flow causes infarction and has enabled us to trace the sequence of events leading to this; but these techniques have added little to our understanding of stroke or extended what was already known from animal work. While it is hoped that the techniques will guide therapeutic intervention, their limited availability means that they can do no more than point the way to what might be of potential value. Similarly, the use of neurotransmitter blockers or labelled transmitters has shown abnormalities in diseases such as Parkinson's disease but has added little to what is already known. The potential for further study is there but I wonder if really new data will be forthcoming. Dementia is another area where PET could be of value but it does not help in separating vascular from non-vascular dementias; I suspect the former are much rarer than previously thought and may well go the way of arteriosclerotic Parkinson's disease, ie largely vanish. Mention has been made of PET in neuropsychology. Comparison of the neuropsychological deficit with metabolism may well help the anatomical map makers and has the potential for separating disconnection syndromes from abnormalities due to loss of cortical grey matter. Overall, PET scanning does not warrant an alpha in the nineteen-eighties but could do better in the nineteen-nineties.

Neurochemistry is another area not covered in the above discussion. The rapid expansion in understanding neuro-transmitter and neuro-modulator physiology led to the description of selective depletion in certain disorders, particularly the dementias. Encouraged by the successes stemming from the discovery of the selective loss of the dopaminergic systems in Parkinson's disease, a discovery now thirty years old, numerous laboratories looked at a number of dementias and found reductions in a variety of transmitters, especially acetylcholine. Therapeutic trials followed using cholinergic agonists, but to no avail. The transmitter schools continue to flourish but one has to wonder whether they are merely producing elegant histological stains or are discovering something more fundamental—probably a mixture of both.

Because of the clinical and social importance of dementia it has attracted the attention of the DNA technologists. Great excitement was engendered by the observation that an amyloid precursor protein is encoded on chromosome 21, since amyloid deposition within the CNS is a constant feature in Alzheimer's disease and some other dementias, including those that are transmissible. It was suggested that in familial Alzheimer's disease a restriction fragment length polymorphism segregates with the precursor protein of the amyloid. The fact that trisomy 21 (Down's syndrome) is associated with Alzheimer's disease of early onset led to the concept that, in some way, a double representation of the amyloid gene played a fundamental

part in the development of Alzheimer's disease. Some of the original observations were unfortunately incorrect; a little extra study rather than rushing into print would have paid dividends. Pressure to publish, a syndrome that has recently become endemic on this side of the Atlantic as well as in the USA, can be counter-productive.

Finally, a recent development in neurophysiology is the observation of Merton and Morton that it is possible to stimulate the CNS electrically (and magnetically) through the intact skin. These workers showed in 1980 that if a high-voltage short-duration current is applied to the scalp, the resistance falls and the cortex can be activated. This technique has been exploited to examine the corticospinal pathways by both physiologists and clinicians. In neurology it is particularly valuable in determining whether these tracts are intact in the unconscious patient subject to cord trauma and to confirm the presence of cord lesions in MS since it is possible to stimulate the CNS at several levels. The technique has also been used, together with sensory evoked potentials, in neurosurgery to guide the hand of the operator and warn him of impending trouble. Hopefully, they will improve the results of delicate neurosurgery, eg upon the brainstem and cord.

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## Sons-in-law

In the 18th century nepotism was expected, not deplored. But it did not always work out, witness the stories of Dr Nicholls and Dr Trinder. Frank Nicholls, son of a London barrister, excelled at Oxford where he gained his doctorate in medicine and became Reader in Anatomy. Elected FRS in 1728, he became FRCP four years later, at the age of 33. As Munk wrote, 'The novelty of his discoveries and the gracefulness of his manner' attracted large audiences to his London lectures. At the College, Nicholls was twice the Goulstonian Lecturer and a long-term Lumleian Lecturer (the lecturer was then appointed for several years to give a course of lectures). He served as Censor in 1735 and again in 1746. He had the good sense to marry in 1743 the youngest daughter of Dr Richard Mead, the most famous physician of the time. Immediately Nicholls gained access to a lucrative fashionable private practice and flourished from then on.

For reasons unstated, but probably malicious, he failed to become an Elect of the College in 1749, a much junior physician being chosen. Understandably Nicholls severed his connection with the College and his father-in-law resigned his own position as an Elect. None of this diminished Nicholls' success in practice and he was physician to George II from 1753 to 1760. 'Tired at length of London and wishing personally to superintend the education of his son' he moved, in 1762, to Oxford where his son John was studying law at Exeter College.

John's friend and fellow law student was Martin Trinder, obviously clever as he graduated Bachelor of Law in 1763 at the age of 16 years. Trinder's friendship with the Nicholls family blossomed and in due course he married Frank Nicholls' daughter. Trinder had taken a degree in civil law at Oxford in 1770 but the thoughts of what his new father-in-law could do for him as a physician took him to Edinburgh and then on to a month in Leiden where he obtained his MD, dedicating his thesis to John

Nicholls. Immediately, Trinder started practice in Romford, then a small Essex market town. There he was the only physician among three apothecaries (a fourth left to join the Dragoons). Attempting to be in the fashion, Trinder wrote of the medicinal qualities of the waters from ten Essex wells. He particularly praised the water from a well in Gidea Park, then owned by Richard Benyon who does not appear to have been asked about it. Gidea Park is on the outskirts of Romford so Trinder would have hoped to have made good use of its waters which 'conveyed a very agreeable sense of freshness' and 'were impregnated with magnesia, Glauber's salt and with sulphur.' The water could be bottled and 'would bear carriage to remote places.' Naturally, Trinder advocated Gidea Park water as a remedy for a variety of ills but was 'sorry to inform the Ladies that tea must be condemned as improper during a course of this water.'

Trinder seems never to have sold a bottle of the water, in Romford or in remote places. He soon moved on to practice in Barnet, where he took Holy Orders. In 1798 he published a pamphlet on *The outward and salutary application of oils on the human body*, styling himself 'The Rev. Dr Trinder . . . a doctor of physick at Leiden . . . who offers to attend patients both at home and abroad.' For good measure, he published a book of sermons. He tried to advocate the water of the Barnet well in 1800 and was back with his oils in 1812. He died in 1818. Poor Frank Nicholls, he must have been disappointed in his son-in-law. Though lawyer, physician and cleric, Trinder seems to have mastered nothing. No wonder it was said of his marriage that 'this connection did not prove harmonious.' Frank Nicholls could be proud of his son John who became a prominent London barrister and a Member of Parliament.

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